

Incidents, Reportable Problems, or Events

1.0 Purpose:

The purpose of this policy is to define the information that requires prompt reporting to the Wright State University Institutional Review Board (hereafter referred to as IRB).

2.0 Scope:

This policy applies to all human subject research for which the IRB acts as the IRB of record.

3.0 Definitions:

3.1 **Unanticipated Problem Involving Risks to Participants or Others (UAP)** means:

- The problem/event/incident is UNEXPECTED in terms of nature, severity, or frequency, given:
 - The research procedures described in the protocol, Investigator Brochure, informed consent document and/or other study related documents; and
 - The characteristics of the subject population being studied; AND
- The information indicates the research places subjects or others at **SERIOUS** risk (as defined below) **or** an increased risk of physical, psychological, economic, legal, or social harm than was previously known or recognized, AND
- The problem/event/incident is RELATED or POSSIBLY RELATED to the procedures involved in the research.

3.2 **Serious** means a problem/event that:

- Results in death;
- Is life-threatening (places the subject at immediate risk of death from an event as it occurred);
- Results in inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth defect; or
- Based on appropriate medical judgement, may jeopardize the subject's health, and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

- 3.3 **Unanticipated Adverse Device Effect** means any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application. Any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
- 3.4 **Prompt Reporting means** reporting of problems or events that are defined in this policy should occur as soon as possible after the Principal Investigator (PI) learns of the event, but in all cases within 10 calendar days. These should be reported via an Incident submission in the IRB electronic submission system.
- 3.5 **Subject/Participant** means as an individual enrolled in a research study that either is conducted at a Wright State/affiliated hospital or that is conducted off-site under the direct supervision of a Wright State/affiliated hospital PI at a non-Wright State/affiliated hospital site.
- 3.6 **Protocol Deviation/Violation** means any alteration/modification to approved research protocol that are under the investigators control and made without prior IRB approval. They are divided into two categories: major (subject to prompt reporting) and minor.
- 3.6.1 **Major:** has the potential to negatively impact subject safety or integrity of study data (ability to draw conclusions from the study data) or affect the subject's willingness to participate in the study. These must be reported promptly.
- 3.6.2 **Minor:** do not have a major impact on either the participants rights, safety, well-being, or the completeness, accuracy, or reliability of the data. These should be reported at renewal/continuing review. It is recommended to report these annually for studies not subject to renewal/continuing review.
- 3.7 **Investigator** means the Project Director/Principal Investigator (PD/PI) and any other person, regardless of title or position, who is responsible for the design, conduct, or reporting of research, or proposing of research, including persons who are subcontractors, collaborators, or consultants. At Wright State this definition includes, but is not limited to, the following roles: Principal investigator, co- investigators, research coordinators, research associates, collaborators, and consultants, and may include research assistants and students as identified by the PD/PI depending on their specific roles and responsibilities.
- 3.8 **Incidents** means any problematic or unanticipated events that are not protocol deviations/violations and that may adversely impact the study participants or the conduct of the study. You must report all major study-related protocol

deviations/violations and incidents to the IRB.

4.0 Policy

Wright State University (Wright State) requires that investigators comply with all applicable local, state, and federal laws and regulations in the conduct of research studies. As part of this requirement, investigators are required to promptly submit to the IRB written reports of certain problems, events, or incidents listed below, including “unanticipated problems involving risks to participants and others.” This policy is established to ensure compliance with applicable regulatory requirements and to assist investigators in understanding when and what new information (reportable problem, event, or incident) must be reported to the IRB.

The PI is ultimately responsible for prompt reporting. Before a study is initiated, the PI should review potential reportable problems/events/incidents based on the protocol (e.g., events that requires prompt reporting to the sponsor) and this policy with all study investigators and have a clear process in place to ensure that potential problems/events/incidents identified by study investigators are reported as soon as possible.

Reporting an event/incident to the IRB does not relieve the PI of his/her obligation to report the event to other agencies such as the FDA or study sponsors when required. Sponsored research agreements may require the PI to notify the sponsor of other adverse events and all unplanned deviations or departures from IRB approved protocol procedures. Sponsor reporting requirements for deviations and/or adverse events may differ from IRB reporting requirements. It is the PI's responsibility to comply with the reporting requirements outlined in the signed contract.

5.0 Procedure

5.1 Incidents or Reportable Problems that Require Prompt Reporting

The IRB requires PROMPT (i.e., ASAP and within 10 calendar days) reporting of the following problems or incidents:

- 5.1.1 Any INTERNAL or EXTERNAL Unanticipated Problem Involving Risks to Participants or Others (as defined above). Note that the VA requires that all events meeting the definition of an Unanticipated Problem involving VA research or personnel be reported to the IRB within 5 business days.
- 5.1.2 Information that indicates a change to the risk to benefit ratio of the research.

For example:

- An interim analysis indicates that participants have a lower rate of response to treatment than initially expected;
- Safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected; or
- A paper is published from another study that shows that an arm of the research study is of no therapeutic value.

- 5.1.3 Change(s) in FDA labeling (e.g., black box warning), withdrawal from marketing, manufacturer alert from the sponsor, or recall of an FDA-approved device, or biologic used in the research
- 5.1.4 Change(s) to the research (without prior IRB approval) taken to eliminate an apparent immediate hazard to a research subject
- 5.1.5 Any major protocol deviation/violation. Examples include, but are not limited to:
- Failure to obtain informed consent (i.e., there is no documentation of informed consent)
 - Informed consent obtained after initiation of study procedures
 - Drug/study medication dispensing error
 - Performing a study procedure not approved by the IRB
 - Failure to perform a required lab test that, in the opinion of the PI, may affect subject safety or data integrity
 - Enrollment of a subject who did not meet all inclusion/exclusion criteria
 - Study visit conducted outside of required timeframe that, that in the opinion of the PI, may affect subject safety
 - Failure to follow safety monitoring plan
- 5.1.6 Unexpected incarceration of a research subject
- 5.1.7 Complaint of or related to a research subject when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team.
- 5.1.8 Any unanticipated adverse device effect (as defined above)
- 5.1.9 Any audit, inspection, inquiry by a governmental agency, or correspondence with a government agency
- 5.1.10 Any written report of a federal agency (e.g., FDA Form 483, Establishment Inspection Report (EIR), Warning Letter)

- 5.1.11 Any written audit report by a sponsor regardless of findings
- 5.1.12 Any internal subject death in a “greater than minimal risk” study, even if “anticipated,” if it occurs within 30 days of a study-related procedure or the administration of a study drug
- 5.1.13 Any breach of confidentiality
- 5.1.14 Violations of Dayton VAMC Information Security Requirements
- 5.1.15 Disclosure of Incidental Findings

All problems, events, or incidents listed above must be reviewed by the PI (or his/her designee) and submitted by the PI or delegated staff using the Incident submission in the IRB electronic submission system. Initial reports to the IRB may be accepted by other means such as e-mail or phone only if the report is of an urgent nature. However, an incident submission still must be submitted as soon as possible in the electronic submission system in such instances.

When making problem/event/incident reports, investigators should take into consideration whether substantive changes in the research or informed consent document may be warranted to protect the safety, welfare, or rights of subjects or others. Any proposed changes must be submitted via the electronic submission system as a modification submission. Examples of substantive changes include:

- Changes to eligibility criteria
- Changes to safety monitoring procedures
- Changes to the informed consent document to describe newly identified risk
- Suspension of enrollment of new subjects
- Suspension or termination of the research

Note: The IRB does not accept sponsor IND/IDE safety reports describing adverse events that have occurred at sites other than those subject to this policy unless the report is of an incident that is: (1) serious; (2) unexpected or unanticipated; (3) related to the investigational drug/device; and (4) suggests that subjects are at an increased risk of harm and as such warrants changes in the research, consent process, or informing subjects. IND/IDE safety reports that warrant changes must be submitted via the electronic submission system as a modification, not an incident submission./.

- 5.2 Reportable Problems, Events, or Incidents that Require Reporting at Renewal/Continuing Review and Study Closure

5.2.1 Minor Protocol Deviations/Violations:

During the conduct of the study all minor protocol deviations must be recorded on the Study Deviation Summary Sheet or other IRB-approved form. Minor protocol deviations must be reported to the IRB at the time of renewal/continuing review or study closure by attaching the form to the appropriate submission in the electronic submission system. For studies not subject to renewal/continuing review, it is recommended that the minor deviations log should be submitted annually. Investigators will receive an annual administrative check-in reminder via email.

Examples of minor or administrative deviations could include follow up visits that occurred outside the protocol required time frame because of the subject's schedule, or blood samples obtained at times close to but not precisely at the time points specified in the protocol.

Please note that FDA device regulations at 21 CFR 812.150(a)(4) require prior approval from the sponsor of all planned deviations, including minor deviations. Planned deviations requested of a sponsor must be submitted for IRB review and approved by the IRB prior to instituting any IDE research planned deviations. The PI must submit a modification to the study via the electronic submission system. For device research, the PI must keep on file a copy of the written approval document from the sponsor when a deviation is granted.

5.2.2 Internal Serious Problems that Do Not Meet Definition of an Unanticipated Problem

Information regarding internal SERIOUS problems that occurred during the previous approval period, but did not meet the PROMPT reporting requirements above, must be submitted as part of the renewal/continuing review submission or study closure submission in the electronic submission system. For studies not subject to renewal/continuing review, it is recommended that incident should be submitted to the IRB at least annually. Investigators will receive an annual administrative check-in reminder via email.

5.2.3 Sponsor Monitoring Reports

Information as to whether monitoring by the sponsor was conducted during the previous approval period must be submitted as part of the renewal/continuing review submission or study closure submission in the electronic submission system. Investigators are required to attach a copy of

any monitoring report in which the monitor required corrective actions to the application being submitted. For studies not subject to renewal/continuing review, it is recommended that these reports should be submitted annually. Investigators will receive an annual administrative check-in reminder via e-mail.

5.2.4 Subject Withdrawals

Subject withdrawal occurs when a subject voluntarily withdraws his or her consent to participate in a study, or when a Principal Investigator (PI) ends a subject's study participation.

During the conduct of the study all subject withdrawals must be recorded. At the time of renewal/continuing review of ongoing research studies and studies in long term follow up, the PI will be asked to provide the IRB with the number of subjects who withdrew from the study (for that review period), and the reasons for withdrawal. For studies not subject to renewal/continuing review, it is recommended that these logs should be submitted annually. Investigators will receive an annual administrative check-in reminder via email.

5.3 IRB Review of Problem/Event/Incident Reports

Each reported problem, event, or incident will be assessed by IRB staff to ensure completeness and to make a preliminary assessment of whether the report meets the Office of Human Research Protection (OHRP) or the Food and Drug Administration's (FDA) definition of unanticipated problem (including those reports not characterized by the PI or sponsor as an unanticipated problem), or when the report represents a serious, unexpected, and related adverse event. Reports of concern are forwarded for prompt review by the IRB Chair or Vice-Chair, who may act on behalf of the IRB with regard to such a review. Review of a problem, event, or incident may require use of a consultant, or assistance from a division or department chair to collect additional information before a determination is made.

The IRB Chair/Vice-Chair is authorized to take immediate action to protect the health and safety of research participants. Such action may take the form of:

- asking the researcher to voluntarily impose a hold on the recruitment of participants to facilitate further inquiry by the IRB and/or institutional officials;
- asking the researcher to voluntarily impose a hold on the recruitment and research intervention to facilitate further inquiry by the IRB and/or institutional officials;
- suspending recruitment or enrollment;
- altering or suspending current interventions; or

- terminating the IRB's approval of the project.

Any such action of the IRB Chair will be documented in the study record immediately. If the IRB Chair imposes a partial or complete suspension, the IRB Chair will promptly (i.e., no later than three business days) report the suspension to the IRB staff. The IRB Chair must report any such action taken to the convened IRB at its next regularly scheduled meeting.

While the IRB is undertaking further inquiry, any voluntary "hold" during the fact-finding period does not constitute a suspension of IRB approval for purposes of the required reporting to external agencies or sponsors.

A convened IRB will generally review reportable problems/incidents occurring on studies under its direct oversight that require prompt reporting as well as reportable problems/incidents that are potential UAPs (internal and external), major protocol deviations/violations, potential serious adverse events, and potential serious and/or continuing noncompliance from studies that are otherwise reviewed via the expedited procedure. The IRB may endorse interim action(s) taken by the Chair, if any, or may take a different action or additional actions. In the event immediate action is not required to protect the health and safety of subjects, any of the above actions must be approved in advance by a vote of the IRB.

In the context of multi-site studies, OHRP further defines internal and external UAPs from the perspective of a particular engaged institution, where internal UAPs are those UAPs experienced by subjects enrolled by the researcher(s) at that institution, and external UAPs are those UAPs experienced by subjects enrolled by researcher(s) at other institutions engaged in the study.

The following may be reviewed by the IRB Chair or Vice-Chair using the Expedited Review mechanism:

- Generally, incidents that do not require prompt reporting to the IRB
- Minor protocol deviations
- Sponsor monitoring reports
- Minor non-compliance, including reports of study lapses
- Subject withdrawal not related to risks and PI is not requesting further follow up

Appropriate action will be taken to address the problem/event/incident. The actions may be taken by the Institutional Official (IO), other senior Wright State/affiliated hospital officials charged with acting, or the IRB. The range of actions includes items listed below, but the list does not preclude taking additional actions as determined on a case-by-case basis:

- Administrative hold on the study pending IRB receipt of further information from the PI in a time period not to exceed 90 days;
- Modification of the protocol;
- Modification of the information disclosed during the consent process;
- Providing additional information to current subjects (this must be done whenever the information may relate to the participant's willingness to continue participation);
- Making arrangements for clinical care outside the research or additional follow-up for subjects;
- Providing additional information to past subjects;
- Requiring current subjects to re-consent to participation;
- Alteration of the frequency of continuing review;
- Observation of the research or the consent process;
- Requiring additional training of the PI, co-investigator and/or other study team members;
- Notification of investigators at other sites;
- Obtaining additional information;
- Termination or suspension of the research.

The IO will be informed when a determination has been made that an incident or problem meets the definition of an unanticipated problem involving risks to participants or others and/or when research is suspended or terminated. The IO will fulfill the requirements to report the action to federal departments or agencies as required by regulation in accord with IRB policy.

If a determination is made that a problem or event does not meet the definition of an unanticipated problem involving risks to participants or others, IO notification is not required.

5.4 Dayton Veterans Affairs (VA) Medical Center Additional Reporting and IRB Review Requirements

VA investigators (aka personnel) must notify the IRB orally immediately upon becoming aware of any local research death that is both unanticipated and related to the research. The IRB must alert the VA Office of Research Oversight (ORO) by e-mail or telephone within two business days after receiving such notification and provide relevant information as requested. The Dayton VA facility Director and the ACOS/R&D must receive concurrent notification. VA investigators must submit the incident submission in electronic submission system to the IRB within five business days of becoming aware of the death.

Within five business days after receiving written notification of the death, the IRB

Chair or a qualified IRB member-reviewer must determine and document whether any actions are warranted to eliminate apparent immediate hazards to subjects.

The IRB must review the death and the determination of the IRB Chair or qualified IRB member- reviewer at its next convened meeting and must determine and document that:

- The death was both unanticipated and related to the research; or
- There is insufficient information to determine whether the death was both unanticipated and related to the research; or
- The death was not unanticipated, and/or the death was not related to the research.

Regardless of the determination above, the convened IRB must also determine and document whether any protocol or informed consent modifications are warranted. If modifications are warranted, the convened IRB must determine and document whether investigators must notify or solicit renewed/revised consent from previously enrolled subjects; and if so, when such notification or consent must take place and how it must be documented.

The IRB must notify the Dayton VA facility Director and the ACOS/R&D of its determinations within five business days of the determinations. The Dayton VA facility Director must report the determinations to ORO within five business days after receiving the IRB's notification.

In cases of unauthorized use, loss or disclosure of VA individually identifiable patient information the Associate Chief of Staff (or equivalent) for Research must immediately notify the VA Facility Director, the R&D Committee, and any relevant research review committee upon discovering, receiving, or otherwise becoming aware of a credible report of an incident regarding any unauthorized use, disclosure, transmission, removal, theft, loss, or destruction of VA research- related protected health information (PHI), individually identifiable private information, or confidential information, as defined by the HIPAA Privacy Rule, the Common Rule, the Privacy Act, or 38 U.S.C. §§5701, 5705, and 7332.

6.0 Records

All records related to this process will be stored and maintained in accordance with any Wright State policy, federal regulations and sponsor requirements associated with the human subject research protocol under review.

7.0 References:

- 45 CFR 46.103(b)(5)
- 45 CFR 46.103(a)
- 45 CFR 46.108
- 45 CFR 46.113
- 21 CFR 56.108(b)(1)
- 21 CFR 56.113
- 21 CFR 312.32
- VA Handbook 1058.01
- 38 CFR 16